

A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

PART 1: DOMESTIC ISSUES

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A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE EXECUTIVE SUMMARY

This *Public Health Action Plan to Combat Antimicrobial Resistance* (Action Plan) was developed by an interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health, and also includes the Agency for Healthcare Research and Quality, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, the Health Care Financing Administration, and the Health Resources and Services Administration.

The Action Plan reflects a broad-based consensus of federal agencies on actions needed to address antimicrobial resistance (AR), which was reached based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. While some actions are already underway, complete implementation of this plan will require close collaboration with all of these partners, a major goal of the process. The plan will be implemented incrementally, dependent on the availability of resources.

The Action Plan provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. This document is Part I of the Action Plan, focusing on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that more specifically address international issues. The Action Plan, Part I (Domestic Issues), includes four focus areas: Surveillance, Prevention and Control, Research, and Product Development. A summary of the Priority Goals and Action Items in each Focus Area follows below. A complete list is found in pages 12-38.

Surveillance

Unless AR problems are detected as they emerge – and actions are taken quickly to contain them – the world may soon be faced with previously treatable diseases which have again become untreatable, as in the pre-antibiotic era. Priority Goals and Action Items in this focus area address ways to:

- ▶ Develop and implement a coordinated national plan for AR surveillance
- ▶ Ensure the availability of reliable drug susceptibility data for surveillance
- ▶ Monitor patterns of antimicrobial drug use
- ▶ Monitor AR in agricultural settings to protect the public's health by ensuring a safe food supply as well as animal and plant health

A coordinated national AR surveillance plan for monitoring AR in microorganisms that pose a threat to public health will be developed and implemented. The plan will specify activities to be conducted at national, state, and local levels, define the roles of participants, promote the use of standardized methods, and provide for timely dissemination of data to interested parties, e.g., public health officials, clinicians, and researchers. Needed core capacities at state and local levels will be defined and supported. When possible, the plan will coordinate, integrate, and build upon existing disease surveillance infrastructure. All surveillance activities will be conducted with respect for patient and institutional confidentiality.

The availability of reliable drug susceptibility data is essential for AR surveillance. The accuracy of AR detection and reporting will be improved through training and proficiency testing programs for diagnostic laboratories and by promoting and further refining standardized methods for detecting drug resistance in important pathogens, including bacteria, parasites, fungi, and viruses. Public and private sector partners will address barriers to AR testing and reporting, e.g., barriers due to changes in healthcare delivery.

A plan to monitor patterns of antimicrobial drug use will be developed and implemented as an important component of the national AR surveillance plan. This information is essential to interpret trends and variations in rates of AR, improve our understanding of the relationship between drug use and resistance, and help identify interventions to prevent and control AR.

Improved surveillance for AR in agricultural settings will allow early detection of resistance trends in pathogens that pose a risk to animal and plant health, as well as in bacteria that enter the food supply. Agricultural surveillance data will also help improve understanding of the relationship between antimicrobial drug and pesticide use and the emergence of drug resistance.

Prevention and Control

The prevention and control of drug-resistant infections requires measures to promote the prudent use of antimicrobial drugs and prevent the transmission of infections (whether drug-resistant or not). Priority Goals and Action Items in this focus area address ways to:

- ▶ Extend the useful life of antimicrobial drugs through prudent use policies that discourage overuse and misuse
- ▶ Improve diagnostic testing practices
- ▶ Prevent infection transmission through improved infection control methods and use of vaccines
- ▶ Prevent and control emerging AR problems in agriculture
- ▶ Ensure that comprehensive programs to prevent and control AR involve a wide variety of non-federal partners and the public and become a part of routine practice nationwide

Prudent drug-use policies will be implemented through a public health education campaign that promotes prudent antimicrobial drug use as a national health priority. Other actions in support of prudent drug use will include reducing inappropriate prescribing through development of guidelines, computer-assisted decision support, consideration of regulatory changes, and other interventions that promote education and behavior change among clinicians, and informing consumers about the uses and limitations of antimicrobial drugs.

Improved diagnostic practices will be promoted, including the use of rapid diagnostic methods to guide drug prescribing, the appropriate use of clinical laboratories, and appropriate testing methods by those laboratories. Improved diagnostic practices will be promoted through guidelines, training, and regulatory and reimbursement policies.

Reduced infection transmission will be addressed through public health campaigns that promote vaccination and hygienic practices such as hand hygiene and safe food handling. Infection control in health care settings will be enhanced by developing new interventions based on rapid diagnosis, improved understanding of the factors that promote cross-infection, and modified medical devices or procedures that reduce the risk of infection.

The prevention and control of AR in agriculture requires 1) improved understanding of the risks and benefits of antimicrobial use and ways to prevent the emergence and spread of resistance; 2) development and implementation of principles for prudent antimicrobial drug use in the production of food animals and plants; 3) improved animal husbandry and food-production practices to reduce the spread of infection; and 4) a regulatory framework to address the need for antimicrobial drug use in agriculture while ensuring that such use does not pose a risk to human health.

Comprehensive, multi-faceted programs involving a wide variety of non-federal partners and the public are required to prevent and control AR. The AR Task Force agencies will ensure ongoing input and review and collaboration with non-federal partners. The appropriate agencies will support demonstration projects that use multiple interventions to prevent and control AR (e.g., through surveillance, judicious drug use, optimized diagnostic testing, immunization practice, and infection control). The Task Force agencies will encourage the incorporation of effective programs into routine practice by implementing model programs in federal health-care systems and promoting the inclusion of AR prevention and control activities as part of quality assurance and accreditation standards for health care delivery nationwide.

Research

Understanding of the fundamental processes involved in antimicrobial resistance within microbes

and the resulting impact on humans, animals, and the environment forms an important basis for influencing and changing these very processes and outcomes. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply.

Priority Goals and Action Items in this focus area address ways to:

- ▶ Increase understanding of microbial physiology, ecology, genetics and mechanisms of resistance
- ▶ Augment the existing research infrastructure to support a critical mass of researchers in AR and related fields
- ▶ Translate research findings into clinically useful products, such as novel approaches to detecting, preventing, and treating antimicrobial resistant infections

Needs in the field of AR research will be identified and addressed through a government-wide external program review. Additional research is needed, for example, on the epidemiology of resistance genes; on mechanisms of AR emergence, acquisition, spread, and persistence; and on the effects of antibiotics used as agricultural growth promotants on microbes that live in animals, humans, plants, soil and water. Further study is also required to determine whether variations in drug use regimens may stimulate or reduce AR emergence and spread. Improved understanding of the causes of AR emergence will lead to the development of tools for reducing microbial resistance, as well as for predicting where AR problems are likely to arise.

A comprehensive research infrastructure will help ensure a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. This will be achieved through the appropriate mechanisms and scientific conferences that promote research on AR. The AR Task Force agencies will work with the academic and industrial research communities to attract AR researchers, prioritize needs, identify key opportunities, and optimize the utilization of resources to address AR problems.

The translation of research findings into innovative clinical products to treat, prevent, or diagnose drug-resistant infections is an area in which the government can play an important role, focusing on gaps not filled by the pharmaceutical industry or by other non-governmental groups. Special efforts will be placed on the identification, development and testing of rapid, inexpensive, point-of-care diagnostic methods to facilitate judicious use of antimicrobials. The AR Task Force agencies will also encourage basic research and clinical testing of diagnostic methods, novel treatment approaches, new vaccines and other prevention approaches for resistant infections.

Product Development

As antimicrobial drugs lose their effectiveness, new products must be developed to prevent, rapidly diagnose, and treat infections. The Priority Goals and Action Items in this focus area

address ways to:

- ▶ Ensure that researchers and drug manufacturers are informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics, and of potential markets for these products (designated here as “AR products”)
- ▶ Stimulate the development of priority AR products for which market incentives are inadequate, while fostering their appropriate use
- ▶ Optimize the development and use of veterinary drugs and related agricultural products that reduce the transfer of resistance to pathogens that can infect humans

Current and projected gaps in the arsenal of AR products and potential markets for these products will be reported to researchers and drug manufacturers through an interagency working group convened to identify and publicize priority public health needs.

The development of urgently needed AR products will be stimulated from drug discovery through licensing. The regulatory process for AR products will continue to be streamlined, and incentives that promote the production and appropriate use of priority AR products will be evaluated in pilot programs that monitor costs and assess the return on the public investment.

The production of veterinary AR products that reduce the risk of development and transfer of resistance to drugs used in human clinical medicine will be expedited through a streamlined regulatory and approval process. As with drugs for the treatment of human infections, pilot programs will be initiated to evaluate incentives to encourage the development and appropriate use of priority products that meet critical animal and plant health needs.

Private and public partners will also evaluate ways to improve or reduce the agricultural use of particular antimicrobial drugs, as well as ways to prevent infection, such as the use of veterinary vaccines, changes in animal husbandry, and the use of competitive exclusion products (i.e., treatments that affect the intestinal flora of food animals).

Top Priority Action Items to Combat Antimicrobial Resistance

(All 11 items have top priority, regardless of their order in the list)

Surveillance

- With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities; the roles of clinical, reference, public health, and veterinary laboratories; and is consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed. (Action Item #2)
- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, in agriculture, and in consumer products. (Action Item #5)

Prevention and Control

- Develop and implement a public health education campaign to promote judicious antimicrobial use as a national health priority. (Action Item #27)
- In collaboration with professional societies and other stakeholders, develop, disseminate, and evaluate clinical guidelines that address judicious antimicrobial use (Action Item #29)
- In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs. (Action Item #61)
- Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote judicious drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied effectively on a routine basis and on a large scale and how this application can be done most cost-effectively. (Action Item #66)

Top Priority Action Items - continued on the next page

Research

- Provide to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens.
(Action Item #73)
- Develop a human clinical trials network, involving medical research and health-care institutions, to coordinate and conduct clinical trials addressing AR issues that are difficult to resolve in industry-sponsored studies (e.g., novel therapies, new treatment regimens, and other products and practices).
(Action Item #78)
- Identify, develop, test, and evaluate the impact of new rapid diagnostic methods (e.g., tests for resistance genes including nonculture specimens, point of care diagnostics for patients with respiratory infections and syndromes, and diagnostics for drug resistance in microbial pathogens).
(Action Item #79)

Product Development

- Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines, anti-infective medical devices, and biologics).
(Action Item #82)
- In consultation with stakeholders, economic consultants, and the AR Product Development Working Group, identify ways (e.g. financial and/or other incentives or investments) to promote the development and/or judicious use of priority AR products for which market incentives are inadequate.
(Action Item #83)

INTRODUCTION AND OVERVIEW

BACKGROUND

In the 1940s, the widespread availability of penicillin and the subsequent discovery of streptomycin led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms – viruses, fungi, and parasites – have a remarkable ability to mutate and acquire resistant genes from other organisms and thereby develop resistance to antimicrobial drugs. When an antimicrobial drug is used, the selective pressure exerted by the drug favors the growth of organisms with mutations that allow them to resist the drug's action. The extensive use of antimicrobial drugs has resulted in the emergence of drug resistance that threatens to reverse the miracles of the last half century.

Drug-resistant pathogens are a growing menace to all people, regardless of age, gender, or socioeconomic background. They endanger people in affluent, industrial societies like the United States, as well as in less developed nations. Examples of clinically important microbes that are rapidly developing resistance to available antimicrobials include bacteria that cause pneumonia, ear infections, and meningitis (e.g., *Streptococcus pneumoniae*¹), skin, bone, lung, and bloodstream infections (e.g., *Staphylococcus aureus*^{2,3}), urinary tract infections (e.g., *Escherichia coli*⁴), foodborne infections (e.g., *Salmonella*⁵), and infections transmitted in health care settings (e.g., enterococci⁶ and *Klebsiella*⁷).

For example, up to 30% of *S. pneumoniae* found in some areas of the United States are no longer susceptible to penicillin, and multi-drug resistance is common. Approximately 11% of *S. pneumoniae* are resistant to “third generation” cephalosporin antibiotics, and resistance to the newest fluoroquinolone antimicrobials has already been reported.⁸ Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin, and many are resistant to newer methicillin-related drugs.² Until 1997, vancomycin was the only uniformly effective treatment for *S. aureus* infections. Since 1997, however, strains of *S. aureus* with decreased susceptibility to vancomycin have been reported.^{9,10}

Many other pathogens – including the bacteria that cause tuberculosis¹¹ and gonorrhea,¹² the virus that causes AIDS,¹³ the fungi that cause yeast infections,¹⁴ and the parasites that cause malaria¹⁵ – are also becoming resistant to standard therapies. If we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive – and, in some cases, nonexistent.

Who is at risk?

While anyone may acquire a drug-resistant infection, certain people are at increased risk, including patients in hospitals and children in daycare centers. Drug-resistant infections may be acquired in health care settings (e.g., staphylococcal infections in intensive care units), in the community (e.g. pneumococci acquired from a classmate) and through the food supply (e.g., salmonella acquired from meat or eggs), both domestically and overseas. However, resistant microbes are increasingly appearing in new settings. Methicillin-resistant *S. aureus*, which for 30 years with few exceptions

was a problem only in hospitals, is now occurring in the community.^{3,16}

Financial costs. The costs of treating AR infections place a significant burden on society – a burden that is likely to grow larger as the number of cases of drug-resistant illness increase. Individuals infected with drug resistant organisms are more likely to require hospitalization, to remain in the hospital for a longer time, and to have a poor prognosis. For example, it has been estimated that the in-hospital cost of hospital-acquired infections caused by just six common kinds of resistant bacteria are at least \$1.3 billion per year, in 1992 dollars.¹⁷ This estimate does not include the costs of infections caused by other pathogens, the costs of lost workdays, post-hospital care, or resistant infections in the outpatient or extended care facility settings.

SOLUTIONS: WHAT SHOULD BE DONE? AR will always be with us. The challenge before us is to transform this increasingly urgent threat into a manageable problem. Over the past ten years, the Institute of Medicine,¹⁸ the American Society for Microbiology,¹⁹ other panels of distinguished experts, the Congressional Office of Technology Assessment,¹⁷ and the General Accounting Office^{20, 21} have provided recommendations and options for government action to address the dangers posed by AR. The experts agree that we need to improve surveillance for emerging AR problems, to prolong the useful life of antimicrobial drugs, to develop new drugs, and to utilize other measures, e.g., improved vaccines, diagnostics, and infection control measures to prevent and control AR.

Despite the urgency of the problem, the achievement of these goals has not been simple or straightforward, and accomplishments to date have been insufficient. Monitoring, preventing, and controlling AR requires sustained effort, commitment, and collaboration among many groups in the public and private sectors, and involvement of the general public. It also requires support and leadership from the Federal Government and a willingness to address complex and sometimes controversial scientific, medical, and economic issues.

A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

This *Public Health Action Plan to Combat Antimicrobial Resistance* provides a blueprint for specific, coordinated federal actions to address this emerging threat. The Plan builds upon reports prepared by expert panels in recent years. This document is Part I of the Plan, focusing on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that more specifically address international issues. A National Action Plan to Combat Multi-drug Resistant Tuberculosis has been published previously.²²

Partnerships and Implementation

This plan was developed by an Interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention

(CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), and also includes the Agency for Healthcare Research and Quality (AHRQ), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (DVA), the Environmental Protection Agency (EPA), the Health Care Financing Administration (HCFA), and the Health Resources and Services Administration (HRSA).

The Plan reflects a broadly-based consensus of federal agencies on actions to combat AR. The Plan is based in part on input from a public meeting held in Atlanta, Georgia, in July 1999.²³ Present at the meeting were consultants from a wide variety of groups, including state and local health agencies, universities, professional societies, pharmaceutical and biotechnology companies, health care delivery organizations, agricultural producers, consumer groups, and the public. Implementation of this plan will require collaboration with all of these partners. The plan will be implemented incrementally, as resources and, where needed, new appropriations, become available. The agencies recognize that a number of the items may require either new statutory authority or the adoptions of changes in regulatory requirements. The extent to which such measures may be needed to implement a given action item will be considered by the coordinators and collaborators assigned to each item.

The Plan includes a summary and a list of issues, goals, and action items addressing surveillance, prevention and control, research, and product development. Except where specified, these issues, goals, and action items apply to human AR issues and not to non-human (e.g., agricultural) issues. Agricultural issues refer to the production of animals and plants, as well as fish and other species (aquaculture). For each action item, “coordinator” and “collaborator” agencies/departments are specified. Contingent on available resources, the coordinators will assume the primary responsibility of carrying out the specified action items and the collaborators will assist and/or carry out part of the specified action. The Interagency Task Force will monitor and, if necessary, update the Plan, during the coming years.

THE FOCUS AREAS

I. SURVEILLANCE

INTRODUCTION

Surveillance of AR is critical to provide early warning of emerging problems, monitor changing patterns of resistance, and target and evaluate prevention and control measures.¹ Timely surveillance information is also necessary to assist researchers in developing new drugs and for good patient care. For example, clinicians should be informed of drug resistance problems in their communities that may influence their prescribing decisions and help them avoid treatment failures. In addition, monitoring patterns of antimicrobial drug use is needed to interpret trends and variations in rates of AR, improve understanding of the relationship between drug use and resistance, and help identify preventive interventions.

At present, the United States lacks a coordinated national plan for AR surveillance. Creating a national plan requires collaboration with partners in the public and private sectors. Improved AR surveillance depends upon enhanced epidemiologic and laboratory capabilities at local, state, and national levels, use of standardized and reliable laboratory testing methods, and enhanced use of informatics.

- A. Issue:** The United States lacks a coordinated national plan for surveillance of:
- AR emergence in organism-drug combinations of public health importance
 - Antimicrobial drug use in human and non-human settings
- 1. Goal:** Collaborate with appropriate partners to develop procedures and methods for nationwide surveillance of AR emergence in organism-drug combinations of public health importance

a. Action Items

1

¹Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of data for use in the planning, implementation, and evaluation of public health practice. Desirable qualities of any system include simplicity, flexibility, acceptability, sensitivity, and representativeness. A surveillance system also includes the timely dissemination of these data to persons who can undertake effective prevention and control activities, including clinicians, researchers, laboratorians and public health personnel. MMWR, Guidelines of Evaluating Surveillance Systems, May 6, 1988/37(S5); 118.

- (1) Determine which organisms and susceptibility to specific antimicrobial drugs should be under surveillance and create a mechanism for periodic updating of this list.

Coordinators: CDC, FDA, USDA, EPA

Timeline: Initiated

- (2) **TOP PRIORITY ACTION ITEM** - Identify the components of a national AR surveillance plan and the roles of partners in its design and implementation.

- Determine which surveillance activities should be conducted routinely at national, regional, state, or local levels and which may require specialized projects.

Coordinators: CDC, FDA, USDA

- Define the roles of clinical, reference, public health, and veterinary laboratories at federal, state, and local levels in AR surveillance.

Coordinator: CDC; Collaborators: DoD, DVA, FDA, USDA, HCFA

- Improve coordination of AR surveillance systems at CDC, FDA, and USDA (e.g., identify components for integration).

Coordinators: CDC, FDA, USDA

- Ensure that the national AR surveillance plan is consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed.

Coordinators: CDC, USDA, FDA

Timeline: For entire action item 2, begin within one to two years

- (3) Develop standards and methodologies.

- Develop standards and methodologies for monitoring drug-resistant infections in humans and animals, as well as for monitoring drug-resistant microbes in food products and environmental samples.

Coordinators: CDC, USDA, FDA, EPA

- Develop standardized laboratory methodologies and data elements that allow susceptibility test results and AR surveillance data to be compared across geographic jurisdictions.

Coordinators: CDC, USDA, FDA, EPA

- Similarly, use standardized definitions and methodology (Related Action Item: Surveillance #5) to create an electronic surveillance system that health care institutions can use to compare AR data from other local facilities.

Coordinator: CDC; Collaborators: HCFA, DVA, DoD, HRSA

- Develop standards for reporting quantitative resistance data (e.g., MICs or zone diameters) in ways that will detect decreased susceptibility. This is

necessary because numerical AR test results reported non-quantitatively (e.g., as susceptible, intermediate, or resistant) as “susceptible” may mask an emerging AR problem (i.e., microbes with a small decrease in susceptibility may still be classified as susceptible).

Coordinators: CDC, USDA, FDA

- Assess how current policies on maintaining the confidentiality of medical and veterinary data collected for other purposes relate to procedures for gathering data on antimicrobial resistance. If necessary, develop a comprehensive national confidentiality policy on human and agricultural AR surveillance that includes both patient and institutional confidentiality, is consistent with confidentiality policies applied to other forms of surveillance and research data, and that recognizes the differences in human and animal agriculture surveillance programs.

Coordinator: CDC; Collaborators: DVA, HCFA, DoD, FDA, USDA

Timeline: For entire action item 3, initiated

(4) Address additional surveillance issues unique to AR.

- Conduct post-marketing surveillance for the development of resistance to critical antimicrobial drugs. Surveillance should be linked to information on drug use, and criteria should be developed to allow a prompt response to a finding of increased resistance related to a specific pattern of use (e.g. consumer and professional alerts, enhanced education, labeling changes, or restrictions on use).

Coordinators: FDA, CDC, USDA

- Facilitate the collection on AR surveillance data on pathogens for which cultures are not routinely obtained, either because the infections are empirically treated without laboratory diagnosis or because they are diagnosed with non-culture tests.

Coordinator: CDC

Timeline: For entire action item 4, begin within one to two years

2. Goal: Collaborate with appropriate partners to develop procedures and methods for nationwide surveillance of antimicrobial drug use in human and non-human settings

a. Action Item

(5) TOP PRIORITY ACTION ITEM - Develop and implement procedures for monitoring antimicrobial drug use in human medicine, in agriculture, and in consumer products.

- Incorporate appropriate confidentiality protections in these procedures
- Link human drug-use data to clinical information (e.g., diagnosis, severity of illness, and outcome)

- Link agricultural drug-use data to species and usage patterns.
 - Assess geographic variations in drug use
Coordinators: CDC, FDA, USDA; Collaborators: EPA, DVA, DoD
Timeline: For entire action item 5, begin within one to two years
- (6) Identify and evaluate methods for collecting (e.g., optimal sampling methods) and disseminating the surveillance data on antimicrobial drug use:
- Identify inexpensive sources of drug use data (e.g., the National Ambulatory Medical Care Survey [NAMCS], the National Hospital Ambulatory Medical Care Survey [NHAMCS], and databases in some health care delivery systems and pharmacies) and evaluate their usefulness for surveillance purposes
Coordinators: CDC, FDA
 - Consider ways that results of periodic drug use surveys could be made available to food animal producers and veterinarians to encourage participation in data collection
Coordinators: CDC, FDA, USDA
Timeline: For entire action item 6, begin within one to two years
- (7) Work with accrediting agencies to address antimicrobial drug-use monitoring as part of quality assurance in health care delivery systems. (Related Action Item: Prevention and Control #67)
Coordinators: CDC, HCFA
Timeline: Begin within one to two years
- (8) Convene a working group to assess the possible need for additional federal regulations to facilitate and protect confidentiality in antimicrobial drug use monitoring programs.
Coordinators: CDC, USDA, FDA
Timeline: Begin within one to two years

B. Issue: Implementation of the national plan for AR surveillance will require:

- Reliable drug susceptibility data
- Adequate capacity and resources at state and local health and agricultural agencies
- An accessible, centralized source of AR data

1. Goal: Promote the consistent and appropriate use of reliable laboratory tests for antimicrobial drug susceptibility

a. Action Items

- (9) Ensure that clinical laboratories that provide data for AR surveillance

purposes have clinical access to and routinely participate in pertinent training and applicable proficiency testing programs with good performance and indicate AR testing methodologies in their surveillance reports (e.g., specific automated methods or manual techniques).

Coordinator: CDC; Collaborator: HCFA

Timeline: Initiated

- (10) Evaluate the performance of licensed, automated AR testing devices in context of changing resistance patterns and update their labeling where appropriate (e.g., changes in quantitative resistance that may make a test result invalid).

Coordinators: FDA, CDC

Timeline: Begin within one to two years

- (11) Work with the National Committee for Clinical Laboratory Standards (NCCLS) further to refine antifungal susceptibility testing methods for yeasts and molds.

Coordinators: CDC, USDA, HCFA

Timeline: Initiated

- (12) Develop and promote standardized clinical, epidemiologic, and laboratory methods for documenting drug resistance among parasites (e.g., lice, Trichomonas, Giardia).

Coordinators: CDC, NIH

Timeline: Begin within three to five years

- (13) Identify ways to overcome economic, legal, and other barriers to appropriate AR testing and to the reporting of results (e.g., reimbursement policies, managed-care practices, cost considerations, empiric treatment recommendations, etc.). (Related Action Item: Prevention and Control #37)

Coordinators: HCFA, HRSA, CDC, AHRQ

Timeline: Begin within one to two years

- (14) Identify a legal mechanism for manufacturers to provide otherwise unavailable drugs to government reference laboratories for the sole purpose of antimicrobial drug susceptibility testing (as part of surveillance) with the understanding that these drugs will not be used for drug discovery purposes.

Coordinator: CDC

Timeline: Begin within one to two years

Coordinators: CDC, AHRQ

Timeline: Begin within one to two years

C. Issue: Monitoring AR in agricultural settings is essential to ensure animal and plant health and a safe food supply

- 1. Goal:** Monitor AR in animal and plant pathogens and in bacteria that can be transmitted to humans through the food supply

a. Action Items

- (19) Expand and enhance coordination of surveillance for drug-resistance in enteric bacteria in sick and healthy humans, and sick and healthy animals on farms, at slaughter, and at retail. This effort may include:
 - Expanding the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS:EB)
 - Comparing AR data on pathogenic and non-pathogenic organisms detected on farms (in sick and healthy animals), at slaughter, and in commercial food products
 - Utilizing these data to monitor the transmission of resistant infections and assess the effectiveness of prevention measures

Coordinators: CDC, FDA, USDA
Timeline: Initiated
- (20) Evaluate the usefulness of monitoring sentinel human populations (e.g., farm, abattoir, fruit and vegetable, and food processing plant workers) and persons in the general community for infection or colonization with resistant enteric bacteria.

Coordinators: CDC, USDA, FDA
Timeline: Begin within three to five years
- (21) Conduct pilot studies to assess the extent and impact of environmental contamination by antimicrobial drug residues and drug-resistant organisms that enter the soil or water from human and animal waste. If appreciable contamination is detected, conduct routine or sentinel surveillance in waste, in surface and ground water, and in soil from agricultural areas in which waste is used for fertilizer. (Related Action Item: Prevention and Control #58)

Coordinators: EPA, CDC, USDA
Timeline: Begin within three to five years
- (22) Gather information on the relationship between antimicrobial pesticide and

herbicide use and the emergence of drug-resistance, by monitoring:

- The prevalence and incidence of drug-resistant organisms in agricultural areas where antimicrobial pesticides are and are not used
- The prevalence of colonization or infection with resistant bacteria in human or animal populations who live or work near orchards or who consume fruit products sprayed (or treated) with antimicrobial pesticides (Related Action Item: Prevention and Control #64)

Coordinators: EPA, CDC, USDA

Timeline: Begin within three to five years

II. PREVENTION AND CONTROL

INTRODUCTION

Prevention and control of drug-resistant infections requires measures to promote the prudent use of antimicrobial drugs (i.e., maximizing their therapeutic effect while minimizing the potential for development of resistance). Prudent antimicrobial drug use can be facilitated by promoting appropriate prescribing by clinicians, informing consumers about the uses and limitations of antimicrobial drugs, and improving diagnostic techniques. Measures to prevent transmission of infection, whether drug-resistant or not, are also important in controlling AR. These include the appropriate use of vaccines and infection control, sanitation, and hygiene measures. Efforts to control drug-resistant infections must become part of everyday practice in health-care settings across the nation, as well as in other settings (e.g., agriculture) in which antimicrobial drugs are used. Partners in many sectors of society, as well as the general public, will need to be involved in this effort.

A. Issue: Overuse and misuse of antimicrobial drugs can hasten the development of resistance and shorten the drug's useful life.

1. Goal: Identify methods for promoting judicious antimicrobial use

a. Action Items

(23) Identify factors that promote or impede judicious drug use in hospitals, extended care facilities, and outpatient settings, working in collaboration with health policy researchers and organizations that can help implement AR prevention and control strategies.

Coordinator: CDC; Collaborators: FDA, AHRQ, DVA, DoD

Timeline: Initiated

(24) Develop judicious drug use policies and evaluate the effectiveness (including cost-effectiveness) of implementing these policies in hospitals and other health-

care delivery settings. Identify ways to increase adherence to judicious use policies proven to be effective.

Coordinator: CDC; Collaborators: AHRQ, FDA, DVA, DoD, HCFA

Timeline: Initiated

- (25) Evaluate the relationship between prescribing behavior and specific antimicrobial drug marketing and promotional practices. Assess the public health effects of these practices.

Coordinators: CDC, FDA

Timeline: Begin within three to five years

- (26) Help individual hospitals and health care systems analyze how the availability of AR data and computer-assisted decision support systems influences prescriber behavior, health outcomes, and costs. This may include the provision of computer software and the establishment of projects that involve the Medicare Peer Review Organizations (PROs).

Coordinator: CDC; Collaborators: HCFA, DVA, DoD

Timeline: Begin within three to five years

2. **Goal:** Promote judicious antimicrobial use through educational and behavioral interventions found to be effective

a. Action Item

- (27) **TOP PRIORITY ACTION ITEM** - Develop and implement a public health education strategy to promote judicious antimicrobial use as a national health priority. The strategy should involve patients, clinicians, educators, industry, and policy makers. Elements of this campaign may include:

- Culturally appropriate educational and behavioral interventions implemented through community-based programs that target
 - Patients and selected populations and communities, such as daycare centers and schools
 - Prescribing clinicians
 - Health care delivery-systems
- A clearinghouse for educational materials (e.g., booklets and CD-ROM presentations) on judicious drug use and AR prevention
- A periodically updated priority list of drug-resistant microorganisms in humans and animals
- A glossary disseminated through CDC Website that defines technical words commonly used in discussions of AR issues

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within one to two years

- (33) Convene an advisory panel or other expert group to consider the management of drugs of last resort for the treatment of resistant infections. Issues for discussion might include:

- Promoting early and wide adoption of prudent use guidelines
- Establishing intensive surveillance of drugs of last resort, with mechanisms for triggering changes in product labeling and use when increased resistance is detected
- Labeling drugs of last resort with the recommendation that they be preferentially used for the treatment of conditions associated with organisms that are resistant to other drugs

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within one to two years

- (34) Convene a working group to examine the impact of federal reimbursement policies for home parenteral antimicrobial treatment on judicious antimicrobial use. Where needed, the working group will make recommendations for modifying these policies.

Coordinator: HCFA; Collaborators: CDC, HRSA

Timeline: Begin within one to two years

- (35) Develop and submit measures for appropriate antimicrobial use to the National Committee for Quality Assurance for inclusion in Health Plan Employer Data and Information Set (HEDIS), which provides comparative data on managed care organizations.

Coordinator: CDC; Collaborator: HCFA

Timeline: Initiated

B. Issue: Improve diagnostic practices can enhance antimicrobial use and patient care.

1. **Goal:** Identify and promote the widespread use of diagnostic testing and reporting strategies that effectively facilitate judicious use of antimicrobial drugs in routine practice

a. Action Items

- (36) Evaluate the potential impact of improved diagnostic tests, including rapid point-of-care tests on antimicrobial drug use and patient care, and assess their financial implications. Take into account tests that distinguish between bacterial and viral infections; tests that identify resistant

pathogens; and tests that distinguish common clinical syndromes such as bacterial sinusitis and acute bacterial otitis media from illnesses with similar manifestations for which antimicrobials are not beneficial. (Related Action Item: Research #79)

Coordinator: CDC; Collaborators: DVA, DoD

Timeline: Begin within one to two years

- (37) Identify economic and other barriers in the health care system (e.g., reimbursement policies by third-party payers, managed care practices, cost considerations, empiric treatment recommendations, etc.) to diagnostic testing that promotes appropriate use of antimicrobials. Develop recommendations that remove disincentives or promote incentives to such testing.

Coordinator: HCFA; Collaborators: CDC, HRSA

Timeline: Begin within three to five years

- (38) In collaboration with professional societies, industry, and other stakeholders, develop guidelines for use by clinicians and clinical microbiology laboratories that address:
- Appropriate specimen collection
 - Performance, interpretation, and reporting of antimicrobial (including antifungal) susceptibility tests performed on clinical specimens
 - Use of in-office (point-of-care) tests for infection, including AR infections

Coordinator: CDC; Collaborator: FDA

Timeline: Begin within three to five years

- (39) In collaboration with professional societies, industry, and other stakeholders, develop guidelines for use by health-care-delivery organizations that address the use of clinical microbiology laboratories.

The guidelines will:

- Promote access to clinical microbiology services by clinicians
- Promote access to appropriate on-site microbiology services in acute care facilities
- Allow physicians to submit specimens to clinical laboratories other than those designated by their health care delivery organization or the patient's insurance company, with appropriate justifications

Coordinator: CDC; Collaborator: HCFA for bullet 2.

Timeline: Begin within three to five years

- (40) Promote the increased performance of direct examination of microbiological specimens (e.g., by Gram stain or other rapid method), in

circumstances where appropriate clinically relevant and reliable information can be garnered, as a readily available point-of-care diagnostic test. This will require working within the framework of the Clinical Laboratory Improvement Amendment (CLIA) regulations and involving medical education and health care delivery organizations.

Coordinator: CDC; Collaborator: HCFA

Timeline: Begin within one to two years

C. Issue: Preventing infection transmission through improved infection control and use of vaccines can help prevent the spread of antimicrobial resistance.

- 1. Goal:** Identify ways to reduce disease transmission in health-care settings and in the community

a. Action Items

- (41) Identify factors that promote transmission of drug-resistant pathogens in health-care facilities, in extended care facilities, and in community settings such as daycare centers. These may include characteristics of the facilities and of the populations that they serve.

Coordinator: CDC; Collaborators: DVA, DoD

Timeline: Initiated

- (42) Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control strategies used in hospitals and other health-care delivery settings.

Coordinator: CDC; Collaborators: DoD, DVA

Timeline: Initiated

- (43) Identify ways to increase adherence to infection-control practices proven to be effective in previous studies.

Coordinator: CDC; Collaborators: DoD, DVA

Timeline: Initiated

- (44) Evaluate the cost-effectiveness and impact on patient care and drug resistance of medical devices that incorporate anti-infective compounds to prevent infection (e.g., anti-infective urinary catheters and prosthetic heart valves). Where appropriate, encourage the clinical use of these devices. (Related Action Item: Product Development #85)

Coordinator: CDC; Collaborators: AHRQ, DoD, DVA, FDA, HRSA, HCFA

Timeline: Begin within three to five years

- (45) Encourage the development of clinical alternatives to those invasive medical procedures and devices that increase the risk of infection in hospitals and other health care setting, e.g., substitution of transcutaneous monitoring of blood oxygen levels of indwelling catheters.

Coordinator: CDC; Collaborators: FDA, DVA

Timeline: Begin within three to five years

- (46) Evaluate the benefits and risks of incorporating antimicrobial, disinfectants, or antiseptic chemicals into consumer products (e.g., soap, toys, kitchen utensils, clothes, paints, plastics, and film preservatives). Consider whether they:

- Have any efficacy in reducing infection
- May play a role in promoting drug resistance

Coordinators: CDC, EPA; Collaborator: FDA

Timeline: Begin within three to five years

2. Goal: Promote infection control through behavioral and educational interventions

a. Action Items

- (47) Conduct a public health campaign to promote hand hygiene and other hygienic practices that prevent the transmission of infectious organisms, in collaboration with professional societies and stakeholders. This campaign may be coordinated with the public health education strategy to promote judicious antimicrobial use described in Action Item #27: Prevention and Control. Components will include:

- Evaluating the curricula of school hygiene courses
- Funding school-based and other programs that promote hand hygiene and other behaviors that prevent infection
- Building on previous campaigns (e.g., ASM's Operation Clean Hands)

Coordinator: CDC

Timeline: Begin within one to two years

- (48) Support ongoing public health education campaigns on food-safety such as FDA and USDA's Fight BAC program,²⁴ whose aim is to educate food producers, suppliers, retailers, and consumers about food safety practices that reduce foodborne infections (including AR infections).²⁵

Coordinators: USDA, CDC, FDA

Timeline: Initiated

- (49) Educate the public about the merits and safety of irradiation as one tool to

reduce bacterial contamination of food.

Coordinator: CDC

Timeline: Begin within one to two years

- 3. Goal:** Optimize the use of vaccines to prevent drug-resistant infections and reduce antibiotic use

a. Action Items

- (50) Support community-based programs that promote and facilitate availability of recommended vaccinations for adults and children.

Coordinator: CDC

Timeline: Initiated

- (51) Identify vaccines useful in reducing drug-resistant infections and evaluate novel methods for improving coverage with these vaccines. For example:
- Evaluate the risks and benefits of allowing certain vaccines for adults (e.g., for pneumococci and influenza virus) to be dispensed by pharmacists without prescription
 - Review and evaluate methods to promote administration of pneumococcal vaccines (e.g., offering vaccination when patients are discharged from the hospital), and encourage the use of methods found to be effective

Coordinator: CDC; Collaborators: DVA, FDA, HCFA

Timeline: Begin within three to five years

- D. Issue:** Prevention and control of drug resistance in agriculture is important to promote animal and plant health, as well as to prevent AR transmission to humans through the food supply or through contact with infected animals.

- 1. Goal:** Improve understanding of the risks and benefits of antimicrobial use, and ways to prevent the emergence and spread of drug resistance, in agricultural settings

a. Action Items

- (52) Evaluate the nature and magnitude of the impact of using various antimicrobial drugs as growth promotants in different species, using current animal husbandry practices. Use this information to assist in risk-benefit assessments of such use.

Coordinator: USDA; Collaborators: CDC, FDA

Timeline: Begin within one to two years

- (53) Conduct additional research to further define the effects of using various veterinary drugs on the emergence of resistant bacteria that infect or colonize food animals of different species, using various animal husbandry practices. Identify risk factors and preventive measures. Assess the associated risk of:
- Transmission of AR infections to humans
 - Clinical disease in humans
 - Transfer of resistance factors from animal flora to human flora
- Coordinators: CDC, USDA, FDA*
Timeline: Initiated
- (54) Conduct epidemiologic and laboratory studies to assess the risk of development and transfer of resistance related to the use of antimicrobial drugs in food and non-food plants, and identify risk factors and potential preventive measures.
- Coordinator: USDA; Collaborators: CDC, FDA, EPA*
Timeline: Initiated
- (55) Develop rapid tests for inspecting fresh commodities like fruit for evidence of contamination with bacteria that are resistant to antibiotics.
- Coordinator: USDA; Collaborators: EPA, FDA, CDC*
Timeline: Begin within one to two years
- (56) Evaluate the effect of current food processing and distribution methods on the emergence and spread of drug-resistant organisms.
- Coordinator: USDA; Collaborators: CDC, FDA*
Timeline: Begin within one to two years
- (57) Identify and evaluate new food pasteurization strategies.
- Coordinator: USDA; Collaborators: FDA, CDC*
Timeline: Begin within three to five years
- (58) Assess the risk of AR emergence and spread due to environmental contamination by antimicrobial drugs or by resistant bacteria in animal and human waste. Collect information on whether environmental contamination by antimicrobial drugs can lead to the development of resistance in bacteria that live in the soil or in water. (Related Action Item: Surveillance #21)
- Coordinators: USDA, CDC, EPA, FDA*
Timeline: Initiated
- (59) Assess the impact of antimicrobial use in companion animals (pets) on

colonization and infection with drug-resistant organisms in the animals and their human household contacts.

Coordinator: CDC

Timeline: Begin within three to five years

2. **Goal:** Promote judicious antimicrobial use in agricultural settings

a. Action Items

- (60) Work with veterinary and agricultural communities to help educate users of veterinary and agricultural antimicrobial about AR issues, and promote the implementation and evaluation of guidelines that address:

- Judicious antimicrobial use in agricultural settings
- Performance and interpretation of antimicrobial susceptibility tests performed on specimens from different species of animals
- Point-of-care tests for infection, including AR infections

Coordinators: USDA, CDC, FDA; Collaborator: EPA

Timeline: Initiated

- (61) **TOP PRIORITY ACTION ITEM** - In consultation with stakeholders, refine and implement the proposed FDA framework²⁶ for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs.

Coordinator: FDA

Timeline: Initiated

- (62) Strongly encourage involvement of veterinarians in decisions regarding the use of systemic antimicrobial drugs in animals, regardless of the distribution system through which the drug is obtained (e.g., regardless of whether a prescription is required to obtain the drug).

Coordinators: FDA, USDA

Timeline: Initiated

- (63) Evaluate the potential impact of making all systemic veterinary antimicrobial drugs available by prescription only.

Coordinators: FDA, USDA

Timeline: Begin within three to five years

- (64) Convene an expert group to consider how to incorporate AR issues into regulations governing the use of pesticides. Invite external experts, stakeholders, and the public to provide input.

Coordinator: EPA

Timeline: Begin within one or two years

E. Issue: Efforts to prevent and control AR emergence and spread must be comprehensive and multi-faceted, and involve a wide variety of non federal partners and the public, and become a part of routine practice nationwide.

- 1. Goal:** Ensure input from non-federal experts on federal efforts to combat antimicrobial resistance

a. Action Items

- (65) Establish an ongoing mechanism to obtain periodic input from external experts on AR issues. This will include ensuring input from stakeholders (e.g., state and local health agencies, the private sector, and the public) in developing and reviewing federal efforts to address antimicrobial resistance.

Coordinators: CDC, FDA, NIH; Collaborators: USDA, EPA, DoD, DVA, AHRQ, HRSA, HCFA

Timeline: Begin within three to five years

- 2. Goal:** Develop and evaluate comprehensive demonstration programs to prevent and control AR

a. Action Items

- (66) **TOP PRIORITY ACTION ITEM** - Support demonstration projects to evaluate comprehensive programs that use multiple interventions to promote judicious drug use and reduce infection rates. These projects will:
 - Assess how interventions found effective in research studies can be applied effectively on a routine basis and on a large scale and how this application can be done most cost-effectively
 - Evaluate the use of these programs in health care systems (federal and non-federal), in the community, and in agricultural settings
 - Involve partnerships with local and state agencies, health care systems, professional societies, community organizations, schools, private industry, and the public

Coordinator: CDC; Collaborators: FDA, DVA, DoD, HRSA, HCFA, USDA

Timeline: Initiated

- 3. Goal:** Incorporate effective AR prevention strategies and programs into routine

clinical practice

a. Action Items

- (67) Utilize federal health care systems (e.g., DoD, VAH, etc.) as model systems for AR surveillance and prevention and control activities involving judicious drug use, optimized diagnostic testing, infection control, and vaccination practice.

Coordinator: CDC; Collaborators: DVA, DoD, HCFA, HRSA

Timeline: Begin within three to five years

- (68) For all health care systems for which federal funds are provided, identify and promote strategies to establish AR prevention and control activities as part of quality monitoring programs

Coordinator: CDC; Collaborators: DVA, DoD, HCFA, HRSA

Timeline: Initiated

- (69) Encourage nationally recognized accrediting agencies such as the National Committee for Quality Assurance (NCQA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), to include accreditation standards that promote efforts to prevent and control AR, including judicious antimicrobial use, infection control, vaccine use, and diagnostic testing. These standards may draw on the findings of existing data and demonstration programs and AHRQ Evidence-Based Practice Centers.

Coordinator: CDC; Collaborators: HCFA, AHRQ

Timeline: Begin within one to two years

III. RESEARCH

INTRODUCTION

Antimicrobial resistance is among the most challenging problems in microbiology, clinical medicine, and public health. Antimicrobial resistance is not one problem, but an overarching term for a whole array of problems. Microbiology, the study of microorganisms, tells us that the processes by which drug resistance occur, are essentially those of evolution. To evolve is to change, and this change is inevitable. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply. Major scientific accomplishments throughout the years have contributed much to the understanding of the fundamental biological processes of AR within microbes and the resulting impact on human, animals, and the environment and provides us the opportunity to influence these very processes and outcomes.

The broad scope of the U.S. research community has a major contribution to make in meeting the challenge of AR in order to reach the goals the AR Task Force has set forth. The research and development of diagnostic tests, new antimicrobial agents, novel therapeutic products, and vaccines and other preventive approaches in response to AR is a multi-step process that begins with basic research discoveries and ends with the availability and use of a new product or implementation of a process. Along this pathway three areas need to be addressed: the identification of gaps and needs in the molecular and cellular understanding of resistance, the infrastructure to support a robust research community, and finally a pathway for movement of research findings into the development of new products.

Through efforts of the Interagency Task Force, important research questions about microbial physiology, ecology, genetics and mechanisms of resistance have been identified. Existing gaps in knowledge and understanding should be addressed to augment the federal and private sector response to the overall problem. Efforts are underway to build and enhance the field of AR research, through increased focus, recognition, and collaboration. The aim is to develop a research infrastructure to support a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. In order to move novel ideas arising at the research bench to useful products or approaches, support of the underlying infrastructure to study and test products and a mechanism to transition to industrial partners is necessary.

This effort will involve federal agencies that conduct, support and promote basic and clinical research in academia and industry and will involve prioritizing needs, identifying key opportunities, recruiting new investigators to the field, and making responsible use of resources to address AR problems.

A. Issue: Specific scientific gaps remain in the understanding of microbial physiology, ecology, genetics and mechanisms of resistance.

1. Goal: Address existing research needs and identify new ones

a. Action Items

- (70) Additional research is needed to enhance the understanding and assess the impact of:
- Mechanisms of AR emergence, acquisition, spread, persistence, and decline, with special regard to multi-drug resistant organisms
 - Emergence and transfer of resistance genes among microorganisms *in vivo*, including epidemiologic factors
 - Effects of preventive, therapeutic, and growth promoting agents on the micro biota of animals, plants, soil, and aquatic environments

- Host factors and immune modulators (e.g., cytosine) in clinical resistance to treatments for opportunistic infections
- Variations in antimicrobial use patterns that may affect the emergence and spread of resistance and the outcome of treatment, including:
 - Differences in duration and dosage in the administration of antimicrobial agents
 - Prophylactic use of antimicrobial (including antibacterial and antifungal) agents
 - Drug combinations used to treat resistant organisms
 - The rotation (cycling) of antimicrobial drugs to prevent the emergence of resistance
 - The determinants of colonization and infection with drug-resistant pathogens

Coordinator: NIH; Collaborators: CDC, FDA, DVA, USDA, EPA, DoD

Timeline: Initiated

- (71) Conduct further government-wide, in-depth, assessment of the scope and composition of AR research to identify research opportunities.

Coordinators: NIH, CDC, FDA, USDA; Collaborators: DoD, DVA, AHRQ, EPA, HCF

Timeline: Initiated

B. Issue: The existing research infrastructure needs to ensure a critical mass of researchers in AR and related fields.

1. **Goal:** Augment the scientific research infrastructure

a. Action Items

- (72) Work with the appropriate peer review structures to ensure that the requisite expertise is applied to the review process to facilitate funding of quality AR research.

Coordinators: NIH, DVA, FDA

Timeline: Begin in one to two years

- (73) **TOP PRIORITY ACTION ITEM** - Provide to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens. Examples include tools such as microbial genome sequences, information on comparative genomics, DNA chip technology, and informatics.

Coordinator: NIH; Collaborators: DoD, USDA, FDA
Timeline: Initiated

- (74) Encourage sharing of AR data between industry and the research community.
Coordinator: NIH; Collaborators: DoD, USDA, FDA
Timeline: Begin in three to five years

2. Goal: Develop a critical mass of researchers in AR

a. Action Items

- (75) Bring new researchers into the field, by utilizing appropriate strategies such as training and research opportunities.
Coordinator: NIH; Collaborators: CDC, FDA, USDA, DoD, DVA
Timeline: Initiated
- (76) Organize conferences that address research issues relating to AR.
Coordinator: NIH; Collaborators: CDC, USDA, FDA, DVA, DoD, AHRQ
Timeline: Initiated

C. Issue: Special efforts are needed to translate research findings into medically useful products for human and veterinary use, such as novel antimicrobial therapeutics, diagnostic tests, vaccines and other tools for preventing AR emergence and spread.

1. Goal: Address the governmental role in translating novel ideas into new clinically relevant products, focusing on gaps not filled by pharmaceutical industry and other non-government groups

a. Action Items

- (77) Explore the need to encourage preclinical studies on the toxicology, pharmacokinetics, and pharmacodynamics of novel therapeutic agents for the treatment of multi-drug-resistant pathogens and facilitate the transition of potential products from preclinical to clinical studies leading to development by industry of novel therapeutic agents.
Coordinator: NIH; Collaborators: DoD, DVA, FDA, USDA
Timeline: Begin within one to two years
- (78) **TOP PRIORITY ACTION ITEM** - Develop a human clinical trials network, involving medical research centers and health-care institutions, to coordinate and conduct clinical trials addressing AR issues that are difficult to resolve in industry-sponsored studies, including:

- Novel therapies
- Existing antimicrobials administered in treatment regimens and combinations that may not be included in approved indications and dosing schedules
- Other products and practices relevant to the control and treatment of antimicrobial-resistant pathogens including devices, diagnostics, disinfectants, etc.

Coordinator: NIH; Collaborators: CDC, DVA, DoD, FDA

Timeline: Begin within one to two years

2. **Goal:** Develop rapid, inexpensive, point-of-care diagnostic methods to facilitate judicious use of antimicrobials.

a. Action Items

- (79) **TOP PRIORITY ACTION ITEM** - Identify, develop, test, and evaluate the impact of new rapid diagnostic methods. Such methods should include:

- Tests for resistance genes that are associated with drug resistance including non-culture specimens
- Rapid point-of-contact diagnostics for patients with viral respiratory infections and clinical syndromes such as otitis media, sinusitis, and pneumonia
- Rapid methods for detecting drug resistance among fungi, parasites, and mycobacteria

Coordinators: NIH, FDA; Collaborators: DoD, USDA, CDC, AHRQ, DVA

Timeline: Initiated

3. **Goal:** Develop new products and strategies to prevent and treat colonization and infection with resistant organisms in patients, prevent transmission of resistant infections in the community, and prevent AR emergence

a. Action Items

- (80) Encourage basic research in support of the development and appropriate use of vaccines. Vaccines are needed to:

- Prevent prevalent viral infections that predispose to bacterial infection or are mistaken for bacterial infections and are inappropriately treated with antibacterial agents (e.g., influenza virus)
- Prevent colonization, infection, and transmission of resistant organisms such as enterococci and staphylococci
- Prevent common bacterial infections (*S. pneumoniae*, nontypable

Haemophilus influenzae) to reduce antibacterial use

Coordinators: NIH, FDA; Collaborators: CDC, DoD, DVA, USDA

Timeline: Initiated

- (81) Encourage basic research in support of novel approaches to preventing or treating infections with resistant organisms. Novel approaches may include:

- Bacteriophage therapy
- Active (vaccine) and passive (antibody, hyperimmune globulin) immunization
- Host-derived antimicrobial agents
- Non-antibiotic antimicrobials with broad or nonspecific anti-infective activities (e.g., defending and non-specific immunostimulants)
- Microbial ecology

Coordinator: NIH; Collaborators: DoD, DVA, FDA, USDA, CDC

Timeline: Initiated

IV. PRODUCT DEVELOPMENT

INTRODUCTION

New products are not being developed rapidly enough to address increasing microbial resistance. Needed products include not only new classes of antimicrobials able to kill otherwise resistant organisms, but also vaccines and anti-infective devices with the potential to prevent infections as well as improved diagnostic tools to aid in appropriate use of therapeutics. With respect to antimicrobial drugs, each new agent represents a major investment by a pharmaceutical company, which must shepherd the product through pre-clinical studies and clinical testing, followed by large and expensive clinical trials. Pharmaceutical companies may be reluctant to invest extensive resources in the development of drugs, such as those antimicrobials targeted to resistant organisms, which are often given for short time periods to small numbers of patients. Manufacturers are similarly concerned that judicious use policies may limit sales and profits. On the other hand, when a drug is used widely, allowing recovery of costs and profitability, resistance may develop more rapidly and shorten the useful life of the drug.

Due to these economic realities – as well as to scientific limitations and a lag in the perception of a need for new agents – very few novel antimicrobial drugs have reached the market for several years. A major aim of this interagency effort is to work with the private sector to explore and test innovative ways to address these issues. Approaches to be considered include providing incentives (and overcoming disincentives) to promote and assist the development of important products to address AR.

Product development is also a very important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to encourage

the development and use of veterinary drugs and agricultural practices that are unlikely to stimulate resistance to important human drugs or spread resistant pathogens to humans. Again, increased attention also needs to be turned to strategies to prevent infections of animals (e.g., vaccines, changes in husbandry) and to the improved use of existing and new products.

A. Issue: Researchers and drug manufacturers need to be better informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, diagnostics, and of potential markets for these products.

1. **Goal:** Provide a systematic assessment of the current status and projected future needs for AR products.

a. Action Items

(82) TOP PRIORITY ACTION ITEM - Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines, anti-infective medical devices, and biologics). The Working Group will:

- Obtain input from stakeholders, including pharmaceutical companies, physicians, epidemiologists, and microbiologists, on which products are needed
- Include experts in the non-medical disciplines (e.g., engineering and remote sensing, etc.)
- Model future resistance trends, product needs, and potential markets, taking into account AR surveillance data and numbers of patients at high risk of developing drug resistant infections (e.g., increases in immunocompromised patients)
- Evaluate current market incentives for the development of priority AR products (Related Action Item: Product Development #83)
- Reassess AR product priorities on a regular basis

Coordinators: FDA, USDA, CDC; Collaborators: NIH, AHRQ

Timeline: Begin within one to two years

B. Issue: Existing market incentives and regulatory processes may be insufficient to stimulate the development of certain priority AR products while fostering their appropriate use.

1. **Goal:** Investigate and act upon potential approaches for stimulating and speeding the entire AR product development process, from drug discovery through licensing

a. Action Items

- (83) **TOP PRIORITY ACTION ITEM** - In consultation with stakeholders, economic consultants, and the AR Product Development Working Group (Related Action Item: Product Development #82), identify ways (e.g. financial and/or other incentives or investments) to promote the development and/or judicious use of priority AR products for which market incentives are inadequate.
- All such proposals will require careful economic modeling and analysis. New approaches should be used on a trial basis, for limited time periods, and the costs and benefits of incentives used in these pilot programs should be monitored to assess the return on the public investment.
Coordinators: FDA, CDC; Collaborators: USDA, AHRQ
Timeline: Begin within three to five years
- (84) In consultation with academia and industry, consider whether government has a constructive role to play in discovery of drugs and other products targeted to address areas where market incentives are limited and unmet needs exist (e.g., novel antimicrobial drugs targeted to specific resistant organisms). (Related Action Items: Research Issue B)
- Such a role could utilize intramural, extramural or partnership type mechanisms. Products developed under such mechanisms could be licensed commercially either with or without specific stipulations regarding use.
Coordinator: NIH; Collaborators: USDA, FDA, CDC
Timeline: Begin within three to five years
- (85) Continue ongoing approaches that streamline the regulatory process, including clinical trials, to help bring AR products (including drugs, vaccines, diagnostics and devices) to market as efficiently and rapidly as possible, while still assuring their safety and efficacy.
- This might involve use of an expedited process in which certain drugs are considered for approval after the completion of Phase 2 clinical trials, in accordance with Subpart E of the Investigational New Drug (IND) regulations. It might also involve defining new surrogate endpoints that indicate a meaningful response benefit over existing treatments for particular infections (e.g., CD4 counts as surrogate markers in the treatment of HIV/AIDS), in accordance with Subpart H of New Drug Application (NDA) regulations.
 - In the case of approvals for anti-infective medical devices, AR concerns will be addressed during the pre-and post-licensing review, to ensure

that these products reduce infection without engendering significant resistance.

Coordinator: FDA; Collaborator: USDA

Timeline: Initiated

C. Issue: The development and use of antimicrobial drugs and related products in agriculture should be optimized to reduce the transfer of resistance to pathogens that can infect humans.

- 1. Goal:** Promote the development and use of new and existing AR products that reduce the risk of the development and transfer of antimicrobial resistance to humans, as well as new approaches to reducing agricultural use of antimicrobial drugs

a. Action Items

- (86) In consultation with stakeholders and expert consultants, identify ways to promote the development of new and alternative veterinary treatments and the improved use of existing therapies that are unlikely to stimulate resistance to drugs in clinical medicine. This action will include consideration of the incentives and approaches listed in Action Item #31 (Prevention and Control), and the implementation of pilot programs to stimulate the development of priority products that meet critical animal health needs.

- Approaches for evaluation should include ways to improve and/or reduce the use of specific antimicrobial drugs, as well as ways to prevent infection, such as vaccines, changes in animal husbandry, and the use of competitive exclusion products (e.g., treatments that affect the intestinal flora of food animals).

Coordinators: FDA, USDA, NIH, CDC, EPA

Timeline: Begin within three to five years

- (87) Streamline the regulatory and approval process for veterinary and agricultural antimicrobial drugs and related products that are unlikely to result in transfer of antimicrobial resistance to humans.

Coordinators: FDA, EPA, USDA

Timeline: Begin within three to five years

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